REMARKS/ARGUMENTS

Claims 1-63 and 65 are pending in this application. In the Office Action, claims 1-60, 62, 63 and 65 are rejected and claim 61 is objected to. Claim 61 has been re-written in independent form to include the recitation of the base claim, i.e., no. 45. No new matter is added by this amendment. Claim 62 has been canceled without prejudice or disclaimer since the subject matter recited therein was added by amendment to claim 45 in a previously filed response. Reconsideration of the application is respectfully requested.

Allowable Subject Matter

Paragraph 14 on pp. 10-11 of the Office Action states that claim 61 would be allowable if re-written in independent form including all of the limitations of the base claim and any intervening claims since the prior art does not teach or suggest orally administering lh-rh amidated at a location which is not naturally amidated.

In response, applicants have re-written the claim in independent form as suggested by the Examiner. Thus, amended claim 61 is now believed to be in condition for allowance.

Declaration Under 37 C.F.R. §1.132

Provided with this Amendment is a "Declaration of Inventor William Stern Under 37 C.F.R. §1.132" filed in support of the patentability of the present invention. The Declaration provides evidence of secondary considerations, including the achievement of unexpectedly improved results (i.e., with regard to bioavailability) with use of the claimed compositions and methods, as well as the satisfaction of a long-felt need. It is submitted to traverse the Examiner's finding(s) that several of the pending claims are 'obvious' to one having ordinary skill in this art pursuant to 35 USC 103.

The declaration demonstrates, through a discussion of experimental evidence provided in applicants' specification, that unexpectedly improved results, i.e., in terms of bioavailability of an active peptide product, are achieved with the use of compositions and methods utilizing orally delivered pharmaceutical products comprising physiologically active peptides that are amidated at a location that is not naturally amidated, as recited in the presently pending claims. The declaration additionally established that the presently claimed materials and methods fulfill a

long-felt need in that the resultant increase in the bioavailability of the subject amidated peptides permits a decrease in the cost-of-goods of peptide-based pharmaceuticals containing the subject peptides, thus allowing for the development of more affordable medicaments.

The Examiner is respectfully requested to take the evidence provided by the declaration into account when reconsidering the various claim rejections based on 35 USC 103.

Objection to the Claims

In ¶2 on p. 2 of the Office Action, the Examiner states that claims 45 and 62 are identical in scope and that claim 62 will be objected to in the event claim 45 is found to be allowable.

Claim 62 has thus been canceled from the application without prejudice or disclaimer since the subject matter recited therein was previously added by amendment to claim 45 in applicants' Amendment mailed May 7, 2007. This amendment is believed to render moot the Examiner's objection to claim 62.

Claim Rejections Under 35 U.S.C. §103

Applicants submit that detailed remarks concerning the prior art references relied upon by the Examiner in support of the various §103 rejections of the present claims have previously been provided in their Amendments dated July 10, 2006 and May 7, 2007. Those arguments are specifically incorporated by reference into this response.

In ¶5 on pp. 3-4, claims 1-8, 12-47, 49-51, 54-60, 62, 63 and 65 are rejected under 35 USC 103 over Stern '918 in view of Habener '712, Balschmidt '021, Barbier '892, EP 878,201 or Neiss '742. This rejection is respectfully traversed.

The Examiner finds that Stern '918 teaches the oral administration of peptides, whereas the remaining, i.e. 'secondary', references teach the existence of amidated peptides, i.e., including peptides amidated at locations which are not naturally amidated. From this disclosure, the Examiner has concluded that it would have been obvious at the time the present invention was made to use the peptides disclosed in such secondary references in the oral administration compositions disclosed in the Stern '918 reference.

The above conclusion is, however, refuted by the evidence provided in the declaration of Inventor Stern provided herewith. Dr. Stern states, for example, in decl. ¶7, that despite years of experience working in this field, neither the relevant literature nor his own experience provided

any impetus for him to suspect that oral administration of a peptide amidated at a location that was not naturally amidated would produce a beneficial effect upon the bioavailability of such amidated peptide(s). Dr. Stern's conclusion is further buttressed, moreover, by the comparative test data involving amidated and non-amidated peptides provided in the specification of the present application and which is discussed, for example, at decl. ¶¶ 8-10.

As further stated by Dr. Stern at decl. ¶11, the finding of increased bioavailability by the process of amidation of a peptide at a position where the peptide is not naturally amidated, in the case of an orally delivered peptide, had not - to his knowledge and belief - been previously disclosed and could not have been either anticipated or obvious to one having ordinary skill in this field based on what was known in the art and/or published in the literature at the time that this application was filed.

Applicants respectfully submit that, giving the declaration its due evidentiary weight under 37 C.F.R. §1.132, the information therein is sufficient to overcome the Examiner's *prima facie* finding, based on his opinion, that it would be obvious to combine the cited references to arrive at the claimed composition and method. The Examiner is, thus, respectfully requested to reconsider and withdraw the rejection of the subject claims under §103.

In ¶6 on pp. 4-5, claims 5 and 48 are rejected for 'obviousness' under 35 U.S.C. §103 over the references relied upon to reject claims 1-8, 12-47, 49-51, 54-60, 62, 63 and 65 (see the discussion above), and further in view of Stern '014. Claim 5 is a composition claim dependent upon claim 1 and claim 48 is a method claim dependent upon claim 45. The claims recite that the orally delivered peptide is prepared as a glycine-extended precursor and subsequently converted to a C-terminal amide group. According to the Office Action, the various secondary references teach peptides amidated at their C-termini, but do not teach synthesizing these peptides by forming glycine-extended precursors and then converting the glycine residue to a C-terminal amide group. Stern '014 is thus added to the combination of references cited to reject the subject claims due to its disclosure regarding this feature. The rejection is respectfully traversed.

Claims 5 and 48 depend, as noted above, on independent claims 1 and 45, respectively. As previously argued by applicants, however, the §103 rejection of the independent claims is based on the Examiner's opinion that one having an ordinary level of skill in the relevant art would find it 'obvious' to introduce one or more of the amidated peptides described in the

secondary references in the oral peptide formulation described in Stern '914. The §1.132 declaration of Dr. Stern, however, evidences that this would not be so, i.e., it would not be obvious to expect an improvement in bioavailability of an active peptide agent by amidating said agent at a location where it is not naturally amidated followed by oral administration of the amidated peptide to a subject in need thereof. In support of their contention (i.e., of non-obviousness), Dr. Stern's declaration presents evidence of unexpectedly improved results with the use of the compositions and methods of the invention (see decl. ¶¶ 8-10) which clearly refutes any finding that one skilled in this art at the time of filing the present application would have been led by the prior art to incorporate into an orally delivered pharmaceutical formulation a peptide amidated at a location not naturally amidated with an expectation of achieving any benefit therefrom, and in particular, the improvement in bioavailability achieved by applicants with the use of the subject amidated peptides.

Based on the above, therefore, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 5 and 48 under §103.

In ¶7 on pp. 5-7, claims 1-47, 49-60, 62, 63 and 65 are rejected under 35 U.S.C. §103 over WO 02/043767 in view of Habener '712, Balschmidt '021, Barbier '892, EP 878,201 or Neiss '742. The rejection is respectfully traversed.

This rejection is similar in nature to that discussed above with regard to claims 1-8, 12-47, 49-51, 54-60, 62, 63 and 65. That is, the Examiner relies upon a primary reference, in this case it is WO 02/043767, to establish that oral peptide formulations are known, whereupon the primary reference is then combined with one or more secondary references disclosing the existence of amidated peptides, including peptides amidated at a location where they are not naturally amidated. These disclosures thus have led the Examiner to conclude that, in his view it would be obvious to modify the formulation disclosed in WO 02/043767 to substitute the amidated peptides disclosed in the secondary references.

However, as discussed above, applicants contend that the improved bioavailability achieved due to substitution of such peptides, i.e., amidated at a location at which they are not naturally amidated, into the formulation described in the primary reference, would have been totally unexpected and thus, non-obvious, to one having an ordinary level of skill in this art at the time the present invention was made. As noted above, the declaration of Inventor Stern provided herewith states, for example, in ¶7, that despite years of experience working in this field, neither

the relevant literature nor his own experience provided any impetus for him to suspect that oral administration of a peptide amidated at a location that was not naturally amidated would produce a beneficial effect upon the bioavailability of such amidated peptide(s). Dr. Stern's conclusion is further buttressed, moreover, by the comparative test data involving amidated and non-amidated peptides provided in the specification of the present application and which is discussed, for example, at decl. ¶¶ 8-10.

As further stated by Dr. Stern at decl. ¶11, the finding of increased bioavailability by the process of amidation of a peptide at a position where the peptide is not naturally amidated, in the case of an orally delivered peptide, had not - to his knowledge and belief - been previously disclosed and could not have been either anticipated or obvious to one having ordinary skill in this field based on what was known in the art and/or published in the literature at the time that this application was filed.

Applicants respectfully submit that, giving the declaration its due evidentiary weight under 37 C.F.R. §1.132, it is sufficient to overcome the Examiner's *prima facie* finding, based on an opinion, that it would be obvious to combine the cited references to arrive at the claimed composition and method. The Examiner is, thus, respectfully requested to reconsider and withdraw the rejection of the subject claims under §103.

In ¶8 on pp. 7-8 claims 5 and 48 are rejected over the references relied upon as discussed above to reject claims 1-47, 49-60, 62, 63 and 65, and further in view of Stern '014. This rejection is made on essentially the same basis as the rejection of claims 5 and 48 raised in ¶6 of the Office Action as discussed above. That is, WO 02/043767 is cited for its disclosure of an oral peptide formulation, while the secondary references - with the exception of Stern '014 - are cited because they disclose various amidated peptides. Stern '014 is cited because it teaches calcitonin made with a C-terminal glycine extension which is enzymatically converted to an amide group

The rejection is, thus, traversed on the same basis as the rejection found in Office Action ¶6. That is, Claims 5 and 48 depend, as noted above, on independent claims 1 and 45, respectively. As argued above by applicants, the §103 rejection of the independent claims is based on the premise that, in the Examiner's opinion, one having an ordinary level of skill in the relevant art would find it 'obvious' to introduce one or more of the amidated peptides described in the secondary references in the oral peptide formulation described in Stern '914. The §1.132 declaration of Dr. Stern, however, evidences that this would not be so, i.e., it would not be

obvious to expect an improvement in bioavailability of an active peptide agent by amidating said agent at a location where it is not naturally amidated followed by oral administration of the amidated peptide to a subject in need thereof. In support of their contention that the subject claims are non-obvious, Dr. Stern's declaration presents evidence of unexpectedly improved results with the use of the compositions and methods of the invention (see decl. ¶¶ 8-10) which clearly refutes any finding that one skilled in this art at the time of filing the present application would have been led by the prior art to incorporate into an orally delivered pharmaceutical formulation a peptide amidated at a location not naturally amidated with an expectation of achieving any benefit therefrom, and in particular, the improvement in bioavailability achieved by applicants with the use of the subject amidated peptides.

Based on the above, therefore, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 5 and 48 under §103.

Claim Rejections Under 35 U.S.C. §102

Claims 1, 6 and 39 are rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Balschmidt et al. USP 5,157,021. According to the Office Action the reference teaches pharmaceutical compositions comprising insulin in which the carboxylic acid groups present in the side chains at residues A4, A17, B13 and B21 are amidated in order to achieve a long-lasting protracted acting insulin analog. The rejection is respectfully traversed.

Claims 6 and 39 both depend from claim 1. The subject claim recites an oral pharmaceutical composition adapted to provide enhanced bioavailability of an orally delivered physiologically active peptide agent, said composition comprising a therapeutically effective amount of said active peptide, wherein said active peptide is amidated at a location that is not naturally amidated.

The Office Action states that, "[a]n intended use limitation, e.g., 'orally delivered' does not impart patentability to product claims where the product is otherwise anticipated by the prior art." Applicants respectfully submit, however, that the recitation of, "an oral pharmaceutical composition" is not a statement of intended use, but rather the word "oral" serves as a limitation in the claim that further defines the invention. That is, defining the claimed composition as an "oral composition" is simply another way of reciting the features of the composition which permit oral delivery of the physiologically active peptide. Those features required to permit such

oral administration of the peptide are clearly set forth in applicants' specification and would be readily understandable to one having ordinary skill in this art. Thus the word "oral" serves as a 'substitute' for specifically reciting the particular features (e.g., pH-lowering agent and/or protease inhibitor, acid-resistant protective vehicle, etc.) needed to render the claimed composition orally administrable. In summary, claiming an "oral pharmaceutical composition" is more than simply a statement regarding an intended use of the composition. It requires that the composition have certain features/attributes which are clearly set forth in the written description of the invention and which, therefore, need not be specifically recited in the claim, i.e., due to the characterization as an "oral composition". In this context, therefore, the term "oral" acts as a limitation rather than simply as a statement of an intended use.

As previously pointed out in applicants' prior responses filed in this application, the Balschmidt '021 reference discloses injectable formulations, rather than the oral formulation as presently recited in the claims. As an formulation formulated for administration via injection, the composition described by the reference does not include all of the features/components required in the present instance for formulating an oral composition. The Balschmidt '021 reference contains no teaching regarding the conversion of the compositions described therein into orally deliverable compositions. Applicants are not arguing that the present invention constitutes either the oral delivery of peptides or the amidation of peptides not naturally amidated. Rather, as recited in the present claims, their invention is directed to the oral administration of a peptide which has been amidated at a location that is not naturally amidated, whereupon this combination of features has been discovered to provide an unexpected enhancement in the bioavailability of the peptide active component.

As the cited combination of features is neither taught nor even suggested in Balschmidt '021 the reference is clearly not anticipatory to applicants' invention. Applicants thus request the Examiner to reconsider and withdraw the §102 rejection of claims 1, 6 and 39 based on the subject reference.

In ¶10 on p. 8 of the Action, claims 1, 4, 5 and 37 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by USP No.5,120,712 to Habener. This rejection is similar in nature to that based on the Balschmidt reference as discussed *supra* in that, according to the Office Action the reference discloses a pharmaceutical composition comprising GLP-1 analogs amidated at the C-terminus.

This rejection is respectfully traversed on the same basis as the rejection above based on Balschmidt. That is, the Office Action states that, "[a]n intended use limitation, e.g., 'orally delivered' does not impart patentability to product claims where the product is otherwise anticipated by the prior art." Applicants reiterate however, that the recitation of, "an oral pharmaceutical composition" is not a statement of intended use, but rather the word "oral" serves as a limitation in the claim that further defines the invention. Defining the claimed composition as an "oral composition" is simply another way of reciting the features of the composition which permit oral delivery of the physiologically active peptide. Those features required to permit such oral administration of the peptide are clearly set forth in applicants' specification and would be readily understandable to one having ordinary skill in this art. The word "oral" thus serves as a 'substitute' for specifically reciting the particular features (e.g., pH-lowering agent and/or protease inhibitor, acid-resistant protective vehicle, etc.) needed to adapt the claimed composition to permit it to be orally administered.

Claiming an "oral pharmaceutical composition" constitutes more than simply stating an intended use of the composition. It requires that the composition have certain features/attributes which are clearly set forth in the written description of the invention and which, therefore, need not be specifically recited in the claim, i.e., due to the characterization as an "oral composition". In this context, therefore, the term "oral" acts as a limitation rather than simply as a statement of an intended use.

As previously pointed out in applicants' prior responses filed in this application, the Habener '712 reference teaches that the formulations described therein may be administered, "intravenously, intramuscularly or subcutaneously", i.e., not orally. Thus, as the reference does not describe oral administration of the composition, there is no reason to believe that the compositions disclosed in Habener '712 are formulated for oral administration, as contrasted to the compositions recited in, e.g., claim 1 of the present application..

As pointed out above, applicants are not arguing that their invention constitutes either the oral delivery of peptides or the amidation of peptides not naturally amidated. Rather, as recited in claim 1 for example, the invention is directed to the oral administration of a peptide which has been amidated at a location that is not naturally amidated, whereupon this combination of features has been discovered to provide an unexpected enhancement in the bioavailability of the peptide active component.

As the cited combination of features is neither taught nor even suggested in Habener '712, the reference is clearly not anticipatory to applicants' invention. Applicants thus request the Examiner to reconsider and withdraw the §102 rejection of claims 1, 4, 5 and 37 based on the subject reference.

Still further, claims 1, 4, 5, 40 and 41 are rejected for anticipation under 35 U.S.C. §102(b) over Barbier et al. U. S. Patent No. 6,110,892 for the reasons set forth in ¶11 on p. 9 of the Office Action. According to the Office Action, the subject reference discloses pharmaceutical compositions comprising amidated fragments of parathyroid hormone (PTH). The rejection relies on the same basis as the rejection based on Balschmidt '021 and that based on Habener '712, i.e., the Examiner's determination not to attribute any patentable weight to the fact that the claimed composition is an "oral composition" whereas Barbier '892 teaches a formulation which is administered via injection and not by an oral route (see, e.g., col. 9, lines 32, 39-44 and 55-59). In response to this rejection, applicants wish to incorporate by reference herein the same arguments made above with regard to the rejections based on Balschmidt and Habener. Thus, those arguments will not be repeated here. Suffice to say, however, that once the characterization of the composition as an "oral composition" is given its appropriate weight, applicants contend it will become apparent that the present claims are in no way anticipated by, or even obvious in light of the disclosure contained in Barbier. The Examiner is thus respectfully requested to reconsider and withdraw the anticipation rejection under §102 based on Barbier '892.

In addition to the rejections noted above, claims 1, 4, 5, 40, 42, 45, 47, 58, 60, 62 and 63 are rejected under 35 U.S.C. §102(e) over Peri et al. U.S. Patent Application Publication No.2004/0023882 for the reasons given in ¶12 on pp. 9-10 of the Office Action. This rejection is also respectfully traversed.

The Peri reference is directed to PTH derivatives which are resistant to skin proteases, as well as to methods for their use. Representative examples of these derivatives are set forth at, for example ¶0067 of the reference. Further according to the reference [see ¶0068], the invention encompasses, *inter alia*, such hPTH sequences provided with amide protecting group(s) at the C-terminal end of the sequence.

The rejected claims are dividable into two 'categories', i.e., (1) those directed to a pharmaceutical composition (nos. 1, 4, 5, 40 and 42); and (2) those directed to a method for enhancing bioavailability of an orally delivered physiologically active peptide agent (nos. 45, 47,

58, 60, 62 (now canceled) and 63). As regards the claims directed to a composition, it is submitted that the C-terminal end of the hPTH sequence described in the reference is a location where amidation naturally occurs and thus the reference does not meet the requirement of claim 1, i.e, wherein the active peptide is amidated at a location that is not naturally amidated. Claim 1 is thus believed to distinguish over the reference, as are claims 4, 5, 40 and 42, which depend directly or indirectly on claim 1 and thus include every feature recited in the independent claim. The Examiner is, therefore, respectfully requested to reconsider and withdraw the rejection of claims 1, 4, 5, 40 and 42.

Turning, then to the method claims rejected under 102(e) over the Peri reference, applicants submit that the invention as recited, e.g., in independent claim 45 is, as noted above, a method for enhancing bioavailability of an orally delivered physiologically active peptide agent which method comprises, *inter alia*, amidating the peptide agent at a location that is not naturally amidated. While applicants will concede that the cited reference does disclose amidated peptide agents, it is submitted that the reference, however, contains no teaching or suggestion that it is likely, or indeed even possible, that the bioavailability of peptide agents can be improved by amidating these agents at a location that is not naturally amidated. Since the reference thus does not teach every element of the claimed invention as recited in claim 45, applicants respectfully request the Examiner to reconsider and withdraw the §102(e) rejection of the subject claim. Moreover, as claims 47, 58 and 60 and 63 each depend, directly or indirectly, upon claim 45 and thus contain all of the limitations in that claim, the dependent claims are believed to be distinguishable over the cited reference for the same reasons as claim 45. Thus, the Examiner should also withdraw the rejection of those claims. As to claim 62, the fact that the subject claim has been canceled is believed to render its rejection moot.

Summary

The claim amendments and arguments provided herein, taken in conjunction with the evidence provided by the Declaration of Inventor Stern Under 37 C.F.R. §1.132 is believed to overcome all of the objections and rejections set forth in the present Office Action. The Examiner is, therefore, respectfully requested to reconsider the objections and rejections and, thus to pass this application through to allowance. If the Examiner believes that an interview would advance the prosecution of this application, he is respectfully invited to telephone

applicants' representative at the number below so that an interview concerning this case can be arranged.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on May 27, 2008:

Mark A. Farley

Name of applicant, assignee or Registered Representative

Signature

May 27, 2008

Date of Signature

Respectfully submitted,

Mark A. Farley
Registration No.: 33,170
OSTROLENK, FABER, GERB & SOFFEN, LLP
1180 Avenue of the Americas
New York, New York 10036-8403
Telephone: (212) 382-0700

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